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A Research Agenda for Environmental Health Aspects of Chromium

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Introduction

The conference participants identified a variety of areas where additional research is required to understand how people are exposed to chromium and their potential risks. These can be divided into the following categories of questions and suggestions for study:

Analytical chemistry: Improvements are needed in standardizing the analysis of chromium species such that it can be replicated in many laboratories. Methods for speciation of chromium in air and water samples appear adequate, but speciation and quantification in complex environmental or biological media require extensive research and development.

Sources of chromium: How does chromium enter the environment and in what form? When chromium-containing materials are incinerated, what determines the proportion in fly ash versus bottom ash? What is the form of chromium when it leaves the stack, and what it is ultimately deposited on the ground or in the lungs? What effect do chromium compounds have on air pollution control devices?

Environmental fate and transport: Traditional questions are complicated by the need to understand speciation of chromium, not only between the trivalent and hexavalent states, but among the different hexavalent salts including the insoluble, soluble, and the partially soluble salts, which appear to be the most significant for human health. The particle size distribution of chromium compounds on dust and soil requires study. The behavior of chromium species in different soils under different conditions varies in a complex fashion, and improved means of predicting are needed. To a certain extent, unique, site-specific studies will be unavoidable.

Exposure and bioavailability: What factors govern the movement of chromium from the environment into the body? What influences the bioavailability of chromium from the different routes of exposure?

Toxicokinetics: How is chromium distributed within the body, and what transformations take place that influence its toxicity, storage, and excretion?

Biomonitoring: What reliable indicators or marks can be developed to assess exposure and body burden of chromium compounds? Do *in vivo* monitoring systems such as X-ray fluorescence or neutron activation offer promise for widescale applicability? Are specific and sensitive adducts formed with macromolecules?

Toxicity: How can we better understand the cellular and subcellular mechanisms by which chromium exerts both pathophysiologic, cytotoxic, and carcinogenic properties? How do extracellular and intracellular binding and redox reactions differ? What role do antioxidants and other ligands play in influencing toxicity? It is desirable to improve the applicability of animal models for chromium toxicity and carcinogenicity.

Epidemiology: How can we improve our understanding of the outcome of exposure to chromium compounds in human populations? What can we learn about the toxicity and carcinogenicity of chromium through routes other than inhalation? What evidence is there that risks from chromium are decreasing or increasing in certain settings?

Risk assessment: For both cancer and noncancer end points, how can we assemble existing and future data on exposure and health effects to improve our understanding of risk to human populations both in the workplace and community? How can we better deal with the uncertainties implicit in both the toxicologic and epidemiologic databases? What are the most reasonable assumptions to be incorporated into the risk assessment?

Environmental cleanup: The issues here are closely linked to risk assessment, exposure assessment and bioavailability. How clean is clean? What procedures can be used to stabilize or remove chromium from the environment? How important is it to reduce the chro-

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mium concentration in soil and water? What must be done to protect workers involved in remediation?

Analytical Chemistry

Storage and preparation of environmental and biological samples often allow or promote interconversion between Cr^{VI} and Cr^{III}. Standardized protocols must be developed and disseminated that will allow qualified research and commercial laboratories to produce accurate and precise analyses for chromium (*1,2*).

In addition, because of the differential toxicity of soluble, partially soluble, and insoluble chromium salts, standardized analytical protocols are required to quantify the proportions of these salts in particular samples.

The digestion and extraction procedures (often involving heat, acid, and oxidizers) used for environmental and biological matrices certainly promote interconversion of chromium species, and procedures must be developed to stabilize the oxidation state while allowing the reduction of complex organic material. Implicit in the development of improved analytic capabilities is the need for standardized quality control methods.

Sources of Chromium

Chromium is ubiquitous in the environment. The main environmental health concerns stem from chromium deposition through industrial wastes—deliberate in the case of chromate slag used for landfills or permitted discharges and accidental in the form of leaks and spills. Much of the industrial discharge is in the form of dissolved chromium released to surface waters. However, there is a major need to understand atmospheric losses of chromium through stacks or in fly ash. Incineration of all sorts (municipal, sludge, hazardous waste) releases chromium, and it is necessary to understand the species that are released and what interchanges occur in the heated plume and subsequently in the atmosphere.

Environmental Fate and Transport

Once chromium has entered the air or water, physical, chemical, photochemical, and biological agents act on it to change its form, properties, and bioavailability, Under some redox conditions, environmental chromium is stabilized in the +6 state. The factors that influence the cationic replacements of the hexavalent chromium salts also need to be investigated. It is still not possible to predict how chromium compounds will behave in soil until the soil environment has been adequately characterized (*3*).

Exposure

The factors that govern the movement of chromium from the environment into the body require extensive investigation. Most important is the bioavailability through inhalation, ingestion, and dermal routes. Environmental contamination of the soils with chromium compounds is of substantial concern, yet the redox environment of soils is often not considered, nor is the underlying grain structure. Public health officials and risk assessors would benefit from a consensus on how to approach this problem.

The bioavailability of chromium in soil is important because childhood ingestion of soil is a major component of risk assessments. The extent to which disturbance of soil creates dust and leads to the reentrainment of chromium into the air requires investigation. The influence of other contaminants, both organic and inorganic, on the binding and bioavailability of chromium needs extensive study. In urban areas, chromium and lead contamination coexist, and their combined effects, particularly in children, need study. To the extent possible, this should become a predictive science so that extensive, site-specific studies are not required.

Toxicokinetics

Physiologically based pharmacokinetic models are assuming increased importance in environmental risk assessment, and this drives our need to better understand the toxicokinetics of chromium. Whether absorbed through the skin, ingested, or inhaled, chromium is distributed via the blood to many tissues. The kinetics depend on solubility of the initial salt and valence as well as the matrix in which the chromium enters the body. Metabolic transformations that influence its toxicity, storage, and excretion must be investigated. The half-lives of the different chromium salts need to be established more precisely. The distribution of chromium in different depots, particularly bone, needs to be ascertained.

Biomonitoring

The mainstay of biomonitoring for metals is usually the measurement of the metal concentration in blood or urine. Occasionally, other tissues or fluids have been used. The ubiquitous presence of chromium in the clinical setting and laboratory affords an unusually high possibility of contamination. Improved procedures for standardizing the collection, transport, and analysis of tissues or fluids is essential, and these must be disseminated to clinical and analytical facilities.

Alternative means of estimating chromium exposure, such as the development of biomarkers, is an attractive research direction, particularly for a substance which is genotoxic. The possibility of using *in vivo* X-ray fluorescence or perhaps total body neutron activation as a means of estimating body burden would be important advances, particularly if they ever became applicable on a population basis. Chromium interacts with macromolecules and affords the opportunity to detect particular kinds of structural changes or adducts with DNA or with proteins such as hemoglobin.

Toxicity

Recent advances in understanding the genotoxicity of chromium raise additional questions in determining how the toxicokinetics of chromium compounds influence the impact on the target cells. There are still gaps in our understanding of the interactions between hexavalent chromium and DNA on the one hand and the development of cancer on the other (*4,5*). Chromium carcinogenicity needs to be related to our understanding of initiation-promotion models (or those models need to be adapted to our understanding of chromium). Research needs to identify whether lung tissue is uniquely susceptible to chromium, or whether similar effects could be anticipated in intestinal cells. Although it is apparent that Cr^{III} is the main genotoxic species, it is still necessary to identify the form(s) that produce other kinds of biochemical and cellular damage.

Moreover, animal modeling needs to be improved, as lung cancer from chromium is one of the very few cases where it has been difficult to develop an animal model for a known human carcinogen. In part this may reflect the different salts (soluble rather than partly soluble) that were used in the early studies, and partly this reflects problems inherent in animal inhalation studies.

Nephrotoxicity is an area that requires additional investigation. Many heavy metals are nephrotoxic, and acute, high-dose exposure to chromium damages the kidney. However, the renal effects of chronic, low-level chromium exposure must be studied, and the markers of this exposure (excretion of low molecular weight proteins) require further characterization.

On the other hand, chromium compounds, particularly hexavalent compounds, are well-known irritants and sensitizers for skin. Dermal toxicity was clearly identified as an area requiring research, particularly because this may be the main adverse health effect to occur in populations with low-level exposure. Among the dermal toxicity questions were: whether, how, and why children are more sensitive than adults, either to sensitization or irritation? Is irritation necessary for sensitization? What proportion of the population can be sensitized to chromium (are all people potentially sensitizable)? Among people who have been sensitized, what is the dose-response curve?

Epidemiology

How can we improve our understanding of the outcome of exposure to chromium compounds in human populations? This requires continued cohort studies in situations with both known levels of exposure and identity of the specific materials to which people are/were exposed. The use of cohort analysis is a valuable tool, particular since process changes have greatly reduced the amount of chromium to which workers have been exposed. Epidemiologic studies, including follow-up of some of the large cohorts currently under investigation, afford the opportunity to determine the attributable risk for different kinds of exposure.

Since smoking is known to be synergistic with other important occupational lung carcinogens such as asbestos and uranium, it is likely that smoking is not just a confounder in previous studies. Future epidemiologic analyses should attempt to take smoking into account, insofar as possible. The use of case-control approaches in comparing chromium workers who get lung cancer with those who do not affords the opportunity to control for smoking.

Risk Assessment

Risk assessment methodology is evolving for both cancer and noncancer end points, and this will effect how we estimate the health risks to human populations both in the workplace and community. We clearly need to understand the potential of chromium compounds to cause intestinal cancer (or for that matter lung cancer) by ingestion. If dermal toxicity and sensitization are major end points, then the population base and dose response for these effects require extensive investigation. The only data apparently available are drawn from industrial cohorts where self-selection may have left only the least susceptible individuals exposed.

Environmental Cleanup

Once risk assessment leads to a decision to remediate chromium contamination, it becomes essential to develop improved procedures for accomplishing cleanup. Should attempts be made to react hexavalent chromium or to stabilize it *in situ*, or should it be recovered and removed? Research is ongoing to improve procedures for water and soil treatment, as well as for preventing the loss of chromium in the first place. Research is required to establish criteria for removal (the famous how clean is clean rubric). Those workers engaged in remediation may turn out to be the ones with the highest level of exposure, and it is necessary to evaluate their risk and to protect them adequately.

Conclusion

Not only is chromium contamination and potential human exposure and disease important in its own right, but it serves as a microcosm for identifying research needs for many other chemical hazards. Research needs span basic mechanistic biomedical investigations, descriptive studies, and experimental approaches in an applied setting.

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